Evaluation of Molecular Markers of Chemical-Induced Cancers

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The extrapolation of findings from rodent bioassays to humans and extrapolation of observations from levels of exposure giving readily detectable effect to levels of public concern remain two of the major areas of controversy in human health risk assessment. Both of these issues are also involved in evaluating chemicals for potential human hazard when short-term assays are used to evaluate the potential hazard of exposures that may extend over the human lifespan. To reduce cost and also to minimize the use of laboratory animals increasing emphasis is being placed on the use of short-term assays including cells and molecular markers. The range of molecular systems available is increasing rapidly and while holding promise for use in larger scale screening require validation. This validation should include comparisons with traditional assay approaches and use of chemicals that are well-recognized as causing cancer in humans or not causing cancer in humans. A candidate carcinogen is vinyl chloride and a candidate non-carcinogen is caprolactam, the only chemical IARC has classified as not likely to be a human carcinogen. The range of assays used should include the chronic rodent bioassay with provision for observation both to two-years and 20% survival of the lowest treated groups. The numbers and size of the treatment groups should be selected to maximize the utility of the data for exposure-dose-response modeling. Provision should be made for collection of tissues at multiple times to provide material for use in molecular assays, both assays currently available and those yet to be developed. Short-term assays being used for screening the High Production Volume Chemicals should also be included. Special attention should be given to obtaining linkages to any past or current studies of human populations exposed to these chemicals.

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Use of biomarker and other mechanistic data to better define the low-dose region of the dose-response relationships in toxicological studies.

Quantitative risk assessment typically involves the establishment of a dose-response relationship; however, it is commonly observed that the region of interest for risk assessment purposes is below the region where a response can be observed. This often requires an extrapolation of the dose-response relationship to the low-dose region, below the range of the data. The risk estimates derived from such extrapolations depend critically on the assumed shape of the dose-response curve in the low-dose region. Improved knowledge of the shapes of typical dose-response relationships for cancer and non-cancer endpoints could therefore lead to improved accuracy in quantitative risk assessment, and in increased confidence in the resulting risk estimates.

Toxicological investigations of the shapes of dose-response relationships have traditionally been limited by the necessity to observe an overt, quantifiable response in a relatively small number of animals. This necessity is commonly addressed by the use of relatively high doses in toxicological studies, relative to the typical region of interest for humans. These high doses can lead to altered patterns of metabolism and elimination, compared to those which prevail at lower doses. Although mechanistically-oriented scientists have long understood this limitation of high-dose studies, the absolute need to observe a response in order to construct a dose-response relationship has nevertheless limited the practical range of experimentation to the high-dose region.

Biomarker studies focusing on the mechanistic events which ultimately lead to an overt toxicological response hold the promise of extending the range of observable response into the low-dose range, which is more relevant to human exposures. Mechanistic biomarker studies should be conducted to better define the shape of the dose-response relationship for common toxicological end-points, using doses low enough to avoid the alterations of metabolism and kinetics which occur at high doses, and sufficient numbers of animals to distinguish between linear, non-linear, and threshold-like responses. The ultimate goal of these studies should be to provide empirical guidance to the risk assessor in selecting the most appropriate dose-relationships to apply for low-dose extrapolation of toxicological data, for both cancer and non-cancer endpoints.

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